Lombok *Haemophilus Influenzae* Type B (Hib) Vaccine Project

Six-Month Report
April 2002–September 2002

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Summary

During the past six months, the study team has worked on various aspects winding down local activities of the study in Indonesia, which will essentially end during the early part of 2003. During the next year, the team will be working intensely on analyzing data, documenting the results of the study, and then preparing various presentations and peer-reviewed papers. The plan is to finish all aspects of the study by September 2003, the end date of the ARIVAC Cooperative Agreement. However, if work continues beyond that point, the Children's Vaccine Program, PATH, and the Association of Preventive Medicine will support their staff to finish the remaining tasks.

Revision and Finalization of Study Endpoint

Radiologic pneumonia cases, the number of which will determine the study endpoint, did not follow normal seasonal patterns during early 2002 and led to the need to extend the estimated study length by several months. Cases were closely tracked during the period and a final end date for gathering data and surveillance among study children was set for December 31, 2002. Since pneumonia cases among vaccinated children will continue to be hospitalized and x-rayed for several months after vaccination, the study was able to terminate vaccination activities in September 2002 without a significant loss in radiologic cases. This early end to vaccination eliminated ongoing difficulties with local approvals and vaccine supplies, and reduced Ministry of Health (MOH) concerns about a repeat of the negative press publicity experienced two years ago.

Approximately 54,000 children total were enrolled in the study over four years, starting in December 1998. The study will continue to provide free hospital care for children with suspected meningitis or severe pneumonia from Hib study villages through December 2002.

Immunogenicity Study

To provide assurance that there were no problems with vaccine handling or potency, an immunogenicity study was conducted in late September to determine the immune response of children who received three doses of the study vaccine. Approval was received from both the Johns Hopkins University Internal Review Board (JHU-IRB) and the Indonesian MOH Ethics Committee. Blood samples were taken from 96 children, 24 from each of the four study color groups. Once the study code is broken, the study team will be able to determine whether the Hib vaccine provided the expected immune response among the Hib-study group. Laboratory analysis of the blood samples will be conducted in France by Aventis Pasteur. Results will be available in mid-2003.

Polymerase Chain Reaction (PCR) Testing

During the next quarter, the Hib study plans to conduct a PCR analysis of cerebrospinal fluid (CSF) specimens collected during the Lombok vaccine study. In the Lombok Hib study, a large number of CSF specimens collected from children with seizures are culture and latex-negative yet have laboratory evidence of a bacterial etiology (elevated white blood cell count or protein,

or decreased glucose). Most of these children received antibiotics before presentation to the hospital. To provide a more accurate estimate of Hib meningitis incidence and the efficacy of Hib conjugate vaccine in preventing Hib, a more accurate determination of bacterial etiology is needed. Culture and latex-negative specimens will be evaluated using PCR technique at the Biomedik research unit in Mataram. A molecular biology consultant from Institute Pasteur/AMP has been recruited as overall technical advisor for PCR. The testing was scheduled to take place in October, but due to political problems it has been rescheduled for January 2003.

Adverse Events Reporting System

The adverse events reporting system was agreed upon and finalized by all study team members. To satisfy requirements by Aventis for international regulatory reporting, the revised system uses both an active reporting systems and a quarterly database review to identify all convulsions and deaths occurring within one week of immunization. Aventis will have full access to this information and be able to use it for regulatory reporting purposes as required. To avoid misinterpretation of data, the Hib study team and the Indonesian MOH will directly report adverse events to the Indonesian regulatory authorities.

Institutional Review Board (Human Subjects Research) Review

The JHU-IRB and the Indonesian Ethical Review Committees reviewed and approved several addenda to the protocol and resolved issues that have been in process for some time:

- Revision to sample size.
- Explanation of field research on maternal attitudes toward infant mortality that was conducted without ethical review.
- Explanation of the unblinding of possible adverse events cases by Aventis.
- Revision of the adverse events system.
- Making amendments to study protocol describing changes in data analysis plan and guidelines for the Data Safety and Monitoring Board (DSMB) including sample size amendment and adverse events amendment mentioned previously.

These submissions were accepted by the IRBs without comment.

Other Activities

During the past six months, other consultants and staff have gone to the field for various purposes. In April, a radiologist from Jakarta made a second visit to the three hospitals to provide an evaluation of the radiology service and suggest improvements in the radiographic image quality.

In June/July, a database specialist, Tracy Fletcher, from PATH spent a month working with Mary Linehan on the various databases, starting the “cleaning” of the data that will be required prior to analysis. This included review and adjustments to the birth survey data, the cost-effectiveness study data, the verbal autopsy validation, and the overall Hib study databases. Her services will be very useful during the coming months as we close down the data collection phase of the study.

Another visit was made to the Lombok site in September by Dr. Larry Moulton, the team biostatistician and a consultant from Johns Hopkins University, to review the current status of the data, and begin the process of designing various analyses. He reviewed the databases and visited the field sites to familiarize himself with the study setting. The staff spent time clarifying the randomization process and describing the way data was collected and checked for errors. He has asked for some minor changes to be made to the database, but overall felt that the data was in good shape.

Dr. Moulton was able to spot several early adjustments and gaps in the data that will help with the later phases.

Cost Study

Exit interviews for the cost study continue to be collected. A visit by the cost-study team to Lombok took place in September and the local team drafted a plan to finish the necessary data collection in the next few weeks. Dr. Maridiati Nadjab, an economist from the University of Indonesia, has taken over some responsibility for supervision of data collection and analysis of the data. She is working closely with Dr. John Molyneaux, the consultant leading the cost study, and the community motivators to move the cost study along. We have nearly completed the data collection and entry for the exit interviews. Still outstanding is collection of the pharmacy data on cost of drugs and entry of the patient logs for 1998 and 2001. The following papers are planned: “Costs of Pneumonia Treatment in Lombok and the Likely Cost-Effectiveness of Pneumonia Vaccines” and “The Costs and Effectiveness of Improved Pneumonia Referrals.”

Publications

A paper entitled “Incidence, demographic and clinical features, and cost for hospitalization due to respiratory syncytial virus lower respiratory illness among children less than 2 years of age in a rural Asian setting,” was accepted by the *Pediatric Infections Disease Journal* and will be published in the February edition. The lead author is Dr. Djelantik.

The *Journal of Tropical Pediatrics* accepted a paper on hospital mortality, lead author Dr. Djelantik, and will be published at some indefinite time in the future.

The paper “Determinants of Infant Death on Lombok Island, Indonesia” was submitted to *Tropical Medicine and International Health.*

Presentations

In May Dr. Agus Sutanto, the Indonesian Provincial team study director, attended the 2002 Annual Conference of the Global Health Council in Washington, D.C. to present study findings on “Optimizing childhood pneumonia referral through community initiatives, Lombok, Indonesia.” The study documented an increase in hospital admissions of pneumonia and meningitis patients from study villages by 59 percent following the introduction of community motivators. The role of the motivators was to educate mothers about the importance of seeking medical care for pneumonia; they also provided in-hospital patient support services. Motivators reduced self-discharge by patients by 30 percent. For the year 2000 to 2001 each motivator was responsible for 47 extra referrals, and we estimate that an estimated 20 excess deaths were prevented. The community motivators have proven to be a successful and popular intervention in

Lombok, and PATH and the MOH are looking at ways to utilize the lessons learned from the Hib Study in future community-based health projects.

Dr. Brad Gessner presented data from the study at an international meeting called *Global Reduction of Hib Disease: What are the next steps?* in Phoenix, Arizona, USA September 22-25, 2002. James Maynard, Mark Steinhoff, and David Mercer also represented the study team at the meeting.

Study Data

The following table provides preliminary study outcome data from the period of December 1998 through August 2002:

HIB STUDY DATA	NUMBER cumulative total December 1998–August 2002
Total immunized children (1 or more dose)	53,991
Hospitalized cases of severe pneumonia	4,902
X-rayed pneumonia cases	4,695
Hospitalized cases of suspect meningitis (convulsions)	580
Cases of probable bacterial meningitis (WHO definition)	77
Hib-positive cases (culture or latex)	10

Financial Information

The MOH was granted additional funding for the final three months of the current Cooperative Arrangement, primarily because of increased costs of hospital care over time. PATH has given a cost extension of the Arrangement beyond the current end date of September 30, 2002, to extend the agreement to September 30, 2003. This will allow the MOH provincial team to complete the last three months of surveillance, and for the key people on the provincial and national teams to participate in the analysis, writing, and presentation tasks of this next year. There is sufficient funding from USAID and the Children's Vaccine Program at PATH to complete this study according to the following timeline.

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Lombok Hib Study

Timeline for study wrap-up

As of September 2002